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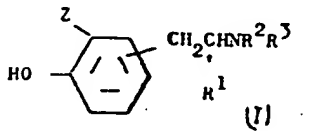
(54) PHENETHYLAMINE DERIVATIVES

(71) We, ALLEN & HANBURYS LIMITED, a British Company of Three Colts Lane, Bethnal Green, London, E.2, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel phenethylamine derivatives possessing useful biological activity and to compositions containing the same.

The present invention provides compounds of the general formula I and physiologically acceptable addition salts thereof:—



(I)

in which R^1 represents a hydrogen atom or a lower alkyl group;

R^2 represents a hydrogen atom or a benzyl or benzhydryl group;

R^3 represents a hydrogen atom or a lower alkyl group or R^3 represents an arylalkyl or aryloxyalkyl radical, which radicals may optionally be substituted by one or more alkoxy or hydroxyl groups;

Z represents a group of formula $—(CH_2)_nY$ in which n has the value of 0, 1 or 2, and Y represents a hydroxyl radical (except when n has the value 0) or an alkoxycarbonyl group of the formula COOR where R represents a hydrogen atom or a lower alkyl group, or Y represents an amido group of formula $CONR^5R^6$ in which R^5 and R^6 are as defined below or a group of formula $—NR^4CONR^5R^6$, NR^4COR^5 or $—NR^4SO_2R^7$ (in which R^4, R^5 and R^6, which may be the same or different and represent hydrogen atoms or lower alkyl groups and R^7 represents a lower alkyl group) except that when n=0 and $Y=NR^4SO_2R^7$, then R^4 is not hydrogen. Preferably at least one of the groups R^1, R^2 and R^3 is other than hydrogen, particularly when Z represents a —COOR group.

By the term "lower alkyl" as used above are meant alkyl radicals which contain from 1 to 6 carbon atoms, and which have a straight or branched chain.

As the compounds of formula I may possess one or more asymmetric carbon atoms, the invention includes all the possible enantiomeric and diastereoisomeric forms of the compounds. The racemic mixtures may be resolved by conventional methods, for example by salt formation with an optically active acid, followed by fractional crystallisation.

The compounds of the invention have useful actions on the cardiovascular system.

Thus, for example, the compound 5-{2-[1-methyl-3-phenyl propyl)amino]-ethyl}salicylamide hydrochloride, ($Z=—CONH_2$, $R^1=R^2=H$, $R^3=CHCH_2CH_2Ph$ with CH_3) causes a dose dependent constriction of isolated artery preparations within a dose range of 1 mg/ml to 1 µg/ml. In addition these concentrations also prevent the subsequent constrictor activities of applied spasmogens, such as noradrenaline and 5-hydroxy-trypt-

amine. Its use is therefore indicated in the treatment of vascular headache (e.g. migraine). In renal hypertensive dogs the compound lowered blood pressure by approximately 45 mm Hg, when administered intravenously at a dose of 1 mg/kg. The heart rate was not affected. The use of the drug in essential hypertension is therefore indicated. The compound 5 - {2 - [(1 - methyl - 3 - phenylpropyl)amino]ethyl} salicylic acid, methyl ester hydrochloride at a dose of 1 mg/kg given intravenously lowered the blood pressure by approximately 40 mm Hg, and the heart rate by approximately 20 beats/minute in renal hypertensive dogs.

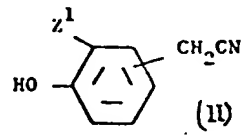
N.B. "Lowered heart rate"

The compounds may be formulated for use in human or veterinary medicine for therapeutic or phophylactic purposes. The invention therefore includes within its scope pharmaceutical compositions comprising as active ingredients compounds of general formula I or physiologically acceptable acid addition salts thereof. Preferred salts include the hydrochloride, sulphate, maleate, acetate, fumarate, lactate and citrate. Such compositions may be presented for use in a conventional manner with the aid of carriers or excipients and formulatory agents as required, and with or without supplementary medicinal agents. These compositions include, for instance, solid or liquid preparations for oral use, suppositories and injections. Oral administration is most convenient in the form of tablets which may be prepared according to conventional methods and may be coated if desired. Injections may be formulated with the aid of physiologically acceptable carriers and agents as solutions, suspensions, or as dry products for reconstitution before use. The active ingredient may be administered at dosages appropriate for the condition being treated, and for the age and weight of the patient, and may vary within a wide range.

Preferred compounds according to the invention are those the preparation of which is described in the Examples. The two compounds specifically mentioned above are particularly preferred.

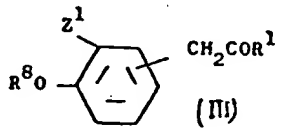
The compounds of the present invention may be prepared by a number of processes.

In one process, the compounds of the invention in which R^1 is a hydrogen atom are prepared by reducing a nitrile derivative of formula II below in which Z^1 represents a group Z or a group convertible thereto, for example by catalytic hydrogenation in acid solution, or by means of a complex metal hydride, for example lithium aluminium hydride. This reduction gives the compounds of formula I in which R^2 and R^3 are both hydrogen. These primary amines of formula I may be converted into the compounds in which R^3 is not a hydrogen atom by condensation with a carbonyl compound, followed by reduction of the azomethine so formed with, for example, a complex metal hydride or hydrogen and a noble metal catalyst.



(II)

In a related process a carbonyl compound of the general formula III is condensed with an amine of formula R^2R^3NH, followed by reduction with for example, hydrogen and a noble metal catalyst, or sodium borohydride.

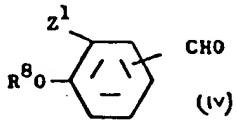


(III)

The radical R^4 represents hydrogen or a benzyl, lower alkyl, or acyl group. When R^4 is not a hydrogen atom it may be removed when desired by hydrolysis or by catalytic hydrogenation.

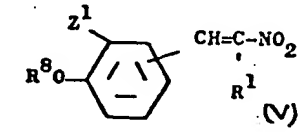
Where R^2 and R^3 in the amine R^2R^3NH are both benzyl groups these steps lead to compounds of the invention (I) where R^2 and R^3 are hydrogen atoms.

The carbonyl compound III may be prepared by several processes, for example by the condensation of an aromatic aldehyde of formula IV,



(IV)

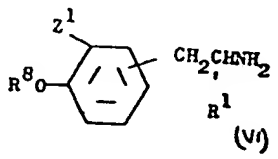
with a nitro compound of formula $R^1CH_2NO_2$, in the presence of a base, to give a nitrostyrene compound of formula V below, which is converted to the compound III on treatment with iron in acid solution.



(V)

The compound of formula V may also be reduced directly with, for example, lithium aluminium hydride or a noble metal catalyst and hydrogen in acid solution followed, if necessary, by conversion of the group —OR^4

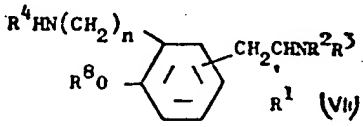
to —OH, to give a compound of the invention.



(VI)

Compounds of the invention where R^3 is not hydrogen can be obtained from compounds of formula VI by reductive alkylation with a suitable aldehyde or ketone. The group Z^1 if other than Z can be subsequently converted to a group Z which may itself be converted a further group Z.

The compounds of the invention in which Z is the group $—(CH_2)_nNR^4COR^5$ may be prepared by acylating an amine of formula VII below (R^4=benzyl, hydrogen or lower alkyl, and R^2 and R^3 are not H) by conventional procedures, with a functional derivative of a carboxylic acid of formula R^5COOH, for example the acid chloride, acid anhydride, or alkyl ester. The protecting group (R^4) may then be removed by catalytic hydrogenolysis and/or hydrolysis with, for example hydrogen iodide or hydrobromic acid.

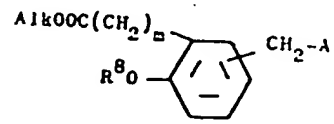


(VII)

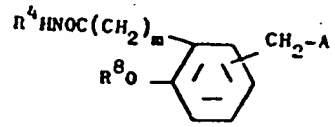
Similarly, reaction of the amine VII (R^2 and R^4 do not represent hydrogen) with a sulphonyl chloride of formula R^7SO_2Cl and when R^4 is other than hydrogen, replacement of R^4 by hydrogen gives the compounds of the invention in which Z is a group of formula $—(CH_2)_nNR^4SO_2R^7$, or with a carbamoyl chloride R^5R^6NCOCl gives the compounds of the invention in which Z is a group of formula $—(CH_2)_nNR^4CONR^5R^6$.

Compounds of the invention in which Z is the group $—(CH_2)_nNR^4CONHR^6$ where one or both of R^5 and R^6 represent hydrogen may also be prepared by acylation of the amine of formula VII, R^2 and R^3 do not represent hydrogen with cyanic acid derivatives and removal of protecting groups. For example, alkyl cyanates of formula R^5NCO give the compounds of the invention in which R^6 is hydrogen, and alkali metal salts of cyanic acid give the compounds in which both R^5 and R^6 are hydrogen.

The amines of formula VII in which n=1 or 2 may be prepared from an alkoxycarbonyl derivative of formula VIII below in which Alk is lower alkyl and in which A represents the side chain $—CHR^1NR^2R^3$, or a group convertible thereto by the methods given above, and m is 0 or 1. This alkoxycarbonyl derivative reacts with ammonia or an amine R^4NH_2 to give the corresponding amide of formula IX, below which is reduced with lithium aluminium hydride.



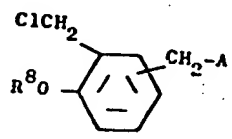
(VIII)



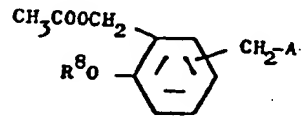
(IX)

The amines of formula VII (n=1) may also be obtained by reacting a compound of formula X below with formaldehyde and hydrogen chloride, optionally in the presence of zinc chloride as a catalyst, to give the chloromethyl compound XI below, followed by reaction with an amine R^4NH_2, and if necessary conversion of the group A. Compounds of formula VII (n=1) where R^4=H can be obtained from the chloromethyl compound XI by condensation with potassium phthalimide followed by removal of the phthaloyl

(X)



(XI)



(XII)

protecting group, for example with hydrazine.

Compounds of the invention in which Z is $—CH_2NR^4SO_2R^7$ (R^4 other than H) may also be prepared from compound XI by reaction with an alkali metal salt of an N-alkylsul-

phonamide $R^2SO_2NHR^1$. For derivatives where $R^1=H$ the sodium salt of an acylsulphonamide R^2SO_2NHAc where Ac is an acyl group may be used, and the acyl and other protecting groups subsequently removed by hydrolysis.

The compounds of formula I in which Z represents a hydroxyalkyl radical of formula $-(CH_2)_n OH$ n=1 or 2 may be prepared from the alkoxycarbonyl derivative of formula VIII above by reduction with lithium aluminium hydride and removal of protecting groups. The hydroxymethyl derivatives may also be obtained from the chloromethyl compounds of formula XI above by dissolving these in sodium acetate to give the corresponding acetoxy compound XII, followed by hydrolysis with dilute acid or alkali, or by reduction with for example lithium aluminium hydride.

It will of course be understood that the reactions used for obtaining the different radicals represented by Z may also be carried out at any convenient stage in the synthesis of the compounds of the invention from the starting materials of formula II, III, IV or V.

The following examples illustrate the invention.

EXAMPLE 1:

5 - [2 - (Benzylamino)ethyl]saligenin acetate (salt)

(i) A solution of 5-(2-aminoethyl)salicylic acid methyl ester hydrochloride (3.6 g) in ethanol (150 ml) containing sodium hydroxide (0.62 g) was stirred with benzaldehyde (1.96 g) for 1 hour at 0°C. Sodium borohydride (0.6 g) was added portionwise over 30 minutes and after a further hour the solution was evaporated. The oily residue was treated with 2N hydrochloric acid and ether and filtered. The resulting white solid was washed with hydrochloric acid and ethyl acetate and dried to give 5 - [2 - benzylamino) - ethyl]salicylic acid methyl ester hydrochloride (3.85 g), m.p. 204°, raised to m.p. 212° when crystallised from methanol-ethyl acetate.

(ii) The basic ester (3.0 g) liberated from the above hydrochloride was added in dry tetrahydrofuran (75 ml) dropwise to a suspension of lithium aluminium hydride (0.75 g) in dry tetrahydrofuran (50 ml). After being stirred for 15 minutes the mixture was treated dropwise with water (2 ml) in tetrahydrofuran (5 ml) filtered and the filtrate was acidified with 2N hydrochloric acid to pH 3. When concentrated the solution deposited a hydrochloride as a white solid. This was neutralised with aqueous sodium bicarbonate and extracted into ethyl acetate to which was added acetic acid (0.3 g) and ether. After 15 hours at 0° the acetate salt precipitated as white crystals, m.p. 117°, which crystallised from acetone. Yield: 75%

EXAMPLE 2:

5 - (2 - Aminoethyl)saligenin

5 - [2 - (Benzylamino)ethyl]saligenin (3.9 g) in methanol (20 ml) and triethylamine (2 g) was added to pre-reduced 10% palladium-charcoal (1 g) in water (20 ml) and the mixture was reduced by hydrogen at room temperature and pressure.

When hydrogenation was complete, catalyst and solvents were removed to leave the primary amine which, when triturated with ethyl acetate, gave white crystals, m.p. 150°. Yield: 79%

EXAMPLE 3:

5 - [2 - (α - Methyl - 3,4,5 - trimethoxy - phenethyl)amino] ethyl saligenin acetate (salt)

This was prepared in 64% yield from the corresponding methyl ester by a method similar to that of Example 1. The compound was a white solid, m.p. 149—153°.

The ester from which it was derived was prepared as described in Example 1 (i) by reductive alkylation using 1 - (3,4,5 - trimethoxyphenyl) - 2 - propanone and catalytic hydrogen (in place of sodium borohydride).

EXAMPLE 4:

5 - [2 - (Benzylamino)propyl]saligenin acetate (salt)

(i) A solution of *p* - [2 - (benzylamino)propyl]phenol (36 g) in glacial acetic acid (2.5 litres), concentrated hydrochloric acid (75 ml) and 36% aqueous formaldehyde (15 ml) was saturated with dry hydrogen chloride and allowed to stand for 7 days at room temperature. When evaporated to dryness the solution gave a residue which was washed with chloroform (250 ml) and dried, to give 4 - [2 - (benzylamino) - propyl] - α - chloro - o-cresol hydrochloride, m.p. 190—192°. Yield: 60%

(ii) Anhydrous sodium acetate (18 g) was added to the above amine (26.4 g) in acetic acid (2.2 litres) and the solution was stirred at 50° for 5 hours and kept at room temperature overnight. The mixture was evaporated to dryness, washed with water, and filtered to give 5 - [2 - (benzylamino)propyl] - saligenin, monoacetate, acetate (salt), m.p. 131°. Yield: 60%.

(iii) The above salt (5 g) in warm dry tetrahydrofuran (500 ml) was added to a suspension of lithium aluminium hydride (5 g) in tetrahydrofuran (250 ml). After 30 minutes wet tetrahydrofuran was added to decompose the complex, and the mixture was evaporated, acidified with dilute hydrochloric acid and neutralised to pH 8 with solid sodium bicarbonate. Chloroform (500 ml) was added, solids were removed by filtration, and the water was separated and re-extracted with chloroform. The combined chloroform solutions were dried (Na_2SO_4) and evaporated to

give the base as a yellow gum. By treating this in ethyl acetate with acetic acid (0.5 ml) the acetate salt (1.9 g) precipitated. Recrystallisation from ethyl acetate gave crystals, m.p. 122°.

EXAMPLE 5:

5 - (2 - Aminopropyl)saligenin acetate (salt)

This was prepared from the product of Example 4 by the method of Example 2. The product crystallised from ethanol-ether, m.p. 148°.
Yield: 67%

EXAMPLE 6:

4 - (2 - Aminoethyl)saligenin acetate (salt)

(a) α - Cyano - 2,4 - cresotic acid, methyl ester

A solution of potassium cyanide (10 g) in water was added to a solution of α-bromo-2,4-cresotic acid, methyl ester, acetate (28.7 g) in dioxan (200 ml). After 2 hours at the reflux the mixture was concentrated and poured into water. The protective acetate group is hydrolysed off by this procedure. The product was extracted into ether which was dried ($MgSO_4$) and evaporated to give the cyano ester (6.7 g) m.p. 87—90°, which recrystallised from ether as colourless crystals, m.p. 101°.

(b) 4 - (2 - Aminoethyl)salicyclic acid methyl ester, hydrochloride.

A solution of the above cyano ester (5.73 g) in methanol (100 ml) was reduced by hydrogen in presence of platinum oxide (0.5 g) in ethanol (50 ml) and saturated methanolic hydrogen chloride (16 ml). The amine hydrochloride (5.5 g) was obtained as a white crystalline solid m.p. 209° when catalyst and solvent were removed.

(c) 4 - [2 - Benzylamino)ethyl]salicylic acid methyl ester hydrochloride

This was prepared from the above amine hydrochloride by the method described in Example 1 (i). The compound was obtained in 60% yield and crystallised from methanol-ethyl acetate as colourless crystals, m.p. 230°.

(d) 4 - [2 - Benzylamino)ethyl]saligenin

Reduction of the ester above, as described in Example 1 (ii) gave the saligenin base which crystallised from ether-cyclohexane as colourless microneedles, m.p. 82°.

(e) 4 - (2 - Aminoethyl)saligenin acetate (salt)

Catalytic hydrogenation of the benzyl derivative above by the method of Example 2 gave a base which was converted to its acetate salt, m.p. 158.5—159.5°.

EXAMPLE 7:

4 - {2 - [(1,1 - Diphenylmethyl)amino] - ethyl}saligenin

(a) 4 - {2 - [1,1 - Diphenylmethyl)amino] - ethyl}salicylic acid methyl ester hydrochloride

A mixture of 4 - (2 - aminoethyl)salicylic acid methyl ester (7.0 g) and benzophenone (14 g) was heated at 170° for 1 hour, cooled and dissolved in ethanol (50 ml). Sodium borohydride (2 g) was added and the solution was stirred at room temperature for 1 hour and evaporated. The residue was treated with excess dilute hydrochloric acid, and the oily precipitate was extracted into chloroform. The dried ($MgSO_4$) solution was evaporated to a residue which on trituration with ether yielded the hydrochloride (11 g), which crystallised from methanol-ethyl acetate as white crystals, m.p. 135°.

(b) 4 - {2 - [(1,1 - Diphenylmethyl)amino] - ethyl}saligenin

Reduction of the above ester using lithium aluminium hydride as in Example 1 (ii) gave the saligenin (in 75% yield) was recrystallised from ether as colourless plates, m.p. 131—132°.

EXAMPLE 8:

[5 - (2 - Aminopropyl)salicyl]urea

(a) N,N - Dibenzyl - *p* - methoxy - α - methylphenethylamine

A mixture of N - benzyl - *p* - methoxy - α-methylphenethylamine[1] (217 g), potassium carbonate (120 g), sodium iodide (30 g) and benzyl chloride (91 ml) in ethyl methyl ketone (500 ml) was stirred and refluxed for 4 hours. The cooled reaction mixture was filtered, and the filtrate evaporated to dryness to leave an oil, which distilled to give the amine (119 g) as a lemon-coloured oil b.p. 185—195°/0.3 mm. A portion was identified as a sulphate, m.p. 182—183°.

(b) N,N - Dibenzyl - 3 - (chloromethyl) - 4 - methoxy - α - methylphenethyl - amine hydrochloride

A solution of the above amine (5.0 g), concentrated hydrochloric acid (7.5 ml), formaldehyde solution (1.5 ml) and glacial acetic acid (50 ml) was saturated with hydrogen chloride. After 10 days at room temperature the deep red solution was evaporated under

[1]G. Regnier, R. Canevari and J. C. Le Douarec, *Bull. Chem. Soc. France*, 1966, 2821.

[1]E. H. Woodruff, J. P. Lambooy and W. E. Burt, *J. Am. Chem. Soc.*, 1940, 62, 922.

reduced pressure to leave an oil that, on standing in contact with dry ether, gave the hydrochloride, m.p. 126°. Recrystallisation from ethyl acetate afforded white microcrystals (2.75 g) m.p. 131°.

(c) N - {5[2 - Dibenzylamino)propyl] - 2 - methoxybenzyl} phthalimide, hydrochloride

The above hydrochloride (1.1 g) was converted into its base and heated on the steam bath for 3 hours with potassium phthalimide (0.45 g) in N,N-dimethylformamide (25 ml). The concentrated mixture was treated with water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, dried (Na_2SO_4) and treated with ethereal hydrogen chloride to give the phthalimido hydrochloride (1.0 g) m.p. 135—137°.

(d) α - Amino - 4 - [2 - dibenzylamino) - propyl] - *o* - cresol, acetate (salt)

A solution of hydrazine hydrate (0.5 ml) and the above phthalimide hydrochloride (1.0 g) in methanol was heated under reflux for 2 hours, and evaporated to dryness. Dilute hydrochloric acid was added and, after removal of precipitated phthalhydrazide, was neutralised with sodium bicarbonate. The base was extracted with ether, the ethereal solution was dried (Na_2SO_4) and evaporated to give the diamine as a yellow oil.

The base was demethylated by refluxing in aqueous hydrobromic acid (48%; 25 ml) for 4 hours. The acidic mixture was neutralised with sodium bicarbonate to yield a buff solid (0.5 g). Treatment of this base with acetic acid in ethyl acetate converted it to an acetate salt m.p. 132—135°, raised to 139—141° on recrystallisation from ethyl acetate.

(e) {5 - [2 - Dibenzylamino)propyl]sali - cyl}urea

A mixture of the acetate salt (0.5 g), above, potassium cyanate (0.4 g) and glacial acetic acid (0.3 ml) in ethanol (10 ml) was heated under reflux for 30 minutes, evaporated and neutralised with sodium carbonate. The mixture was extracted several times with ether, which was dried (Na_2SO_4) and evaporated to yield the urea as a white solid (0.5 g) m.p. 140—150°, which recrystallised from aqueous acetone as white microcrystals, m.p. 154—156°.

(f) [5 - (2 - Aminopropyl)salicyl]urea

Debenzylation of the above urea was carried out as described in Example 2, to afford the primary amine in 50% yield, as a white solid which crystallised from methanol-ethyl acetate as white microcrystals, m.p. 155° (decomp).

EXAMPLE 9:

[5 - (2 - Aminoethyl) - 2 - hydroxyphenyl] - hydrochloride

(a) 4 - {[2 - (1,1 - Diphenylmethyl) - amino]ethyl}phenol hydrochloride

The Schiffs base of tyramine and benzophenone prepared from tyrosine as described by A. F. Al-Sayyab and A. Lawson, *J. Chem. Soc.*, 1968, *C*, 406, was reduced by sodium borohydride in ethanol in a manner similar to that of Example 1 (i). The hydrochloride was obtained in 60% yield as colourless needles, m.p. 235—238°, which could be recrystallised from methanol-isopropanol, m.p. 238—239°.

(b) 4 - {[2 - Benzyl - (1,1 - diphenyl - methyl)amino]ethyl}phenol, hydrochloride

The amine above was benzylated by the procedure described in Example 8 (a). The product was obtained in 88% yield as a cream solid m.p. 200—201°, raised to 218—220° when recrystallised from methanol.

(c) 4 - {[2 - Benzyl - (1,1 - diphenyl - methyl)amino]ethyl} - 2 - nitrophenol, hydrochloride

A suspension of the hydrochloride 9.5 g) of Example 9 (b) in benzene (30 ml) was stirred with 8N nitric acid (25 ml) for 2 hours at room temperature. The mixture was diluted with water and filtered to give a solid which was treated with sodium bicarbonate solution and ether. The ethereal extract was dried, (Na_2SO_4) and evaporated to yield the nitrophenol as a red gum (9 g). A hydrochloride was obtained by the action of ethereal hydrogen chloride to give pale yellow crystals, m.p. 210—212°.

(d) 2 - Amino - 4 - {[2 - benzyl - (1,1 - diphenylmethyl)amino]ethyl}phenol, dihydrochloride

A suspension of Raney nickel (approximately 25 g) in ethanol, was added to a solution of the nitrophenol base above (33 g) in ethanol (500 ml) and hydrazine hydrate (25 ml) was added dropwise with warming. The mixture was refluxed for 1 hour, filtered and evaporated to dryness. The residue was extracted into ether which was washed with water and dried (Na_2SO_4). Addition of ethereal hydrogen chloride precipitated the dihydrochloride (25 g) as a buff solid, which recrystallised from methanol-ethyl acetate to give a white solid, m.p. 185—188° (decomp).

(e) [{5 - [2 - Benzyl - (1,1 - diphenyl - methyl)amino]ethyl} - 2 - hydroxy - phenyl] urea hydrochloride

The base from the above dihydrochloride was converted into the urea by the method described in Example 8 (e) and gave a hydrochloride, m.p. 200—201°.

(f) [5 - 2 - Aminoethyl) - 2 - hydroxy - phenyl]urea hydrochloride

Catalytic hydrogenolysis as in Example 2 afforded the primary amine hydrochloride

which crystallised from methanol-ethyl acetate as cream needles, m.p. 185—186°.

EXAMPLE 10:

N - [5 - 2 - Aminopropyl)salicyl]methane - sulphonamide

(a) N - {5 - [2 - Dibenzylamino)propyl] - salicyl} methanesulphonamide

A solution of α - amino - 4 - [2 - di - benzylamino)propyl] - o - cresol acetate salt (mentioned in Example 8 (d)) (2 g) in pyridine (35 ml) was treated with methanesulphonyl chloride (0.41 ml) in pyridine (10 ml) with ice-cooling. After 3 days at room temperature the mixture was evaporated and the residue basified with sodium bicarbonate and extracted into ethyl acetate. The dried extracts were evaporated to leave a yellow oil which was purified by chromatography down a silica column, eluting with ethyl acetate.

The desired base (0.8 g) was an oil [TLC (thin layer chromatography) (SiO_2-EtOAc): Rf 0.9] and was converted by treatment with hydrogen chloride in ether to a white hydrochloride, which crystallised from methanol-ethyl acetate as colourless microcrystals, m.p. 219—220°.

(b) N - [5 - (2 - Aminopropyl)salicyl] - methanesulphonamide

Catalytic hydrogenolysis of the benzyl groups of the above base gave the primary amine as an oil, which was identified by its spectra and equivalent weight.

EXAMPLE 11:

5′ - {(3 - p - Methoxyphenyl - 1 - methyl - propyl)amino]ethyl} - 2′ - hydroxyform - anilide

(a) 5′ - {[2 - Benzyl - (1,1 - diphenyl - methyl)amino]ethyl - 2′ - hydroxy - formanilide

A solution of 2 - amino - 4 - {[2 - benzyl - (1,1 diphenylmethyl) - amino] - ethyl}phenol (mentioned in Example 9) (17 g) in ethyl formate (150 ml) was refluxed for 5 days and evaporated. The residue crystallised from ether-light petroleum (b.p. 40—60°) as pale yellow needles, m.p. 100—104°.

(b) 5′ - {[(3 - p - Methoxyphenyl - 1 - methylpropyl)amino]ethyl} - 2′ - hyd - roxy-formanilide

A solution of the above base (2.0 g) and 4 - (p - methoxyphenyl) - 2 - butanone (1.0 g) in ethanol (50 ml) was hydrogenated in the presence of 10% palladium-charcoal (0.6 g) and 5% platinum-charcoal (0.6 g) catalysts. When reduction was complete the catalysts and solvent were removed to leave an oil. The base was separated by addition of acetic acid and removal of non-basic material by trituration with ether. The base was regenerated when the ether-insoluble acetate was neutralised with sodium bicarbonate solution and extracted into chloroform. The dried extract was evaporated and the formanilide crystallised from benzene as a white solid, m.p. 125°.

EXAMPLE 12:

4 - (2 - Benzylaminopropyl)salicylic acid methyl ester, hydrochloride.

(a) α,α - Dihydroxy - 2,4 - cresotic acid, methyl ester, triacetate.

A cold solution of chromium trioxide (18 g) in concentrated sulphuric acid (20 ml), acetic anhydride (100 ml) and glacial acetic acid (150 ml) was added slowly, over 2 hours, to a stirred solution of 2,4-cresotic acid, methyl ester, acetate (10 g) in acetic anhydride (200 ml). The temperature of the reaction mixture was kept between —10 to —15° during the addition and for a further 2 hours. Isopropanol was then added to remove excess oxidising agent. The reaction mixture was concentrated to a small volume, quenched with ice-water, and extracted with chloroform. The chloroform was washed with 8% sodium bicarbonate solution, dried and evaporated to yield the ester triacetate, m.p. 96° (crystallising from methanol) in 40% yield.

(b) 4 - (2 - Nitroprop - 2 - enyl) - sali - cylic acid, methyl ester

Ammonium acetate (2.5 g) was added to a solution of α,α - dihydroxy - 2,4 - cresotic acid, methyl ester, triacetate (5.0 g) in nitroethane (200 ml) at 80°, and the reaction temperature raised to 100° for 4 hours. Concentration of the solution, and crystallisation of the residue from methanol gave 4 -(2 - nitroprop - 2 - enyl)salicylic acid, methyl ester (m.p. 134—5°) in 82% yield.

(c) 4 - Acetonyl - salicylic acid, methyl ester

Iron filings (10 g), ferric chloride (0.4 g) and concentrated hydrochloric acid (5 ml) were added to a solution of the above nitropropene (4.9 g) in ethanol (75 ml) and water (175 ml) and the reactants heated under reflux for 6 hours. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure. The product was extracted into ethyl acetate, washed with 8% sodium bicarbonate, brine, and dried ($MgSO_4$). Concentration of the solution gave an orange solid, which distilled under reduced pressure to afford 4 - acetonyl salicylic acid, methyl ester as a pale yellow solid m.p. 42—44° in 85% yield.

(d) 4 - (2 - Benzylaminopropyl) - salicylic acid, methyl ester, hydrochloride.

Triethylamine (1.2 g) and benzylamine (1.92 g) were added to a solution of 4-acetonyl-salicylic acid methyl ester 2.5 g) in methanol (100 ml) and the solution heated under reflux for 2 hours. The solution was hydrogenated, with pre-reduced Adams cata-

lyst (0.35 g) until the theoretical quantity of hydrogen had been absorbed. Concentration of the solution, after removal of the catalyst, gave a yellow oil which was dissolved in ether. Addition of excess 2N hydrochloric acid gave the required product as a white solid. Crystallisation from methanol-ethyl acetate afforded the hydrochloride as colourless needles m.p. 216—218° in 70% yield.

EXAMPLE 13:

5 - {2 - [(1 - Methyl - 3 - phenylpropyl) - amino]ethyl} salicylic acid, methyl ester hydrochloride

Treatment of 5 - (2 - aminoethyl)salicylic acid methyl ester (7.8 g) with 4 - phenyl - 2-butanone (6.7 g) as described in Example 1(i) but using catalytic hydrogen in place of sodium borohydride, gave the basic ester which was converted to its hydrochloride, m.p. 199—200°.

EXAMPLE 14:

5 - {2 - [(1 - Methyl - 3 - phenylpropyl) - amino]ethyl} salicylamide hydrochloride

The product ester from Example 13 (1.4 g) in methanol (50 ml) and ammonia solution (d. 0.880; 20 ml) were allowed to stand at room temperature for 5 days. The mixture was evaporated and the residue triturated with dilute hydrochloric acid to give the amide hydrochloride (1.0 g) m.p. 168—169°.

The following are examples of intermediates that can be processed to compounds of the invention by methods analogous to those described above.

EXAMPLE 15:

3 - (Aminomethyl) - N,N - dibenzyl - 4 - benzyloxy) phenethylamine dihydrochloride

(a) 5 - (2 - Aminoethyl)salicylamide hydrochloride

A solution of 5 - (2 - aminoethyl) - salicylic acid methyl ester hydrochloride (described in Example 1) (1.9 g) in methanol (25 ml) and aqueous ammonia (d. 0.880; 25 ml) was allowed to stand at room temperature for 20 hours. Evaporation under reduced pressure gave a residue which with methanolic hydrogen chloride afforded the amine hydrochloride which crystallised from methanol-ether as a white solid, m.p. 262—263°.

(b) 2 - (Benzyloxy) - 5 - dibenzylamino - ethyl)benzamide hydrochloride

A mixture of the above primary amine hydrochloride product (4.33 g) sodium carbonate (3.5 g) benzyl chloride (10 ml) and sodium iodide (12 g) in methyl ethyl ketone (100 ml) was stirred at the reflux for 72 hours, cooled and filtered. The filtrate was evaporated and treated with ethereal hydrogen chloride to precipitate the hydrochloride (8.8 g) as a low melting solid, which crystallised from methanol-ethyl acetate as colourless needles, m.p. 211°.

(c) 3 - (Aminomethyl)N,N - dibenzyl - 4 - (benzyloxy) phenethylamine dihydrochloride

A solution of the amide base, liberated by aqueous ammonia from the above hydrochloride product (4.9 g) was added to a stirred warm suspension of lithium aluminium hydride (1.5 g) in tetrahydrofuran (20 ml). After being stirred at the reflux for 17 hours the cooled mixture was treated with water (5 ml), filtered and the filtrate evaporated. The oily residue was dissolved in ether and ethereal hydrogen chloride added, to precipitate the dihydrochloride as a white solid (3.7 g) m.p. 210—212°. Recrystallisation from methanol-ethyl acetate gave colourless needles, m.p. 220—221°.

EXAMPLE 16:

N - {5 - [2 - (Dibenzylamino)ethyl] - 2 - methoxybenzyl} - N - methylmethane - sulphonamide

(a) N,N - Dibenzyl - 3 - (chloromethyl) - 4 - methoxyphenethylamine hydro - chloride

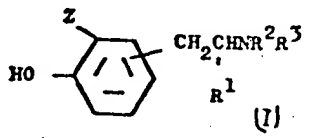
Prepared from N,N dibenzyl - p - methoxyphenethylamine hydrochloride by the method described in Example 8 (b), as colourless crystals from methanol-ethyl acetate m.p. 190—191°.

(b) N - {5 - [2 - Dibenzylamino)ethyl] - 2 - methoxybenzyl} - N - methyl - methanesulphonamide.

The above hydrochloride product (10 g) was basified and added to sodium N-methyl-methanesulphonamide in dimethylformamide (100 ml). After 1 hour at 100° the mixture was cooled and filtered to remove sodium chloride. The filtrate was evaporated, diluted with water and the product extracted with ether. When dried and evaporated the ethereal solution gave an oil (8.5 g) which crystallised from ethanol to afford the sulphonamide as colourless prisms, (5.3 g) m.p. 89°.

WHAT WE CLAIM IS:—

1. Compounds of the general formula I and physiologically acceptable addition salts thereof:



(I)

in which

R^1 represents a hydrogen atom or a lower alkyl group;

R^2 represents a hydrogen atom or a benzyl group;

R^3 represents a hydrogen atom or a lower alkyl group or R^3 represents an arylalkyl or aryloxyalkyl radical, which radicals may optionally be substituted by one or more alkoxy or hydroxyl groups;

Z represents a group of formula $-(CH_2)_nY$ in which n has the value of 0, 1 or 2, and Y represents a hydroxyl radical (except when n has the value 0) or a group of formula $-NR^4CONR^5R^6$, NR^4COR^5, or $-NR^4SO_2R^7$ (in which R^4, R^5 and R^6 which may be the same or different and represent hydrogen atoms or lower alkyl groups and R^7 represents a lower alkyl group) except that when n=0 and $Y-NR^4SO_2R^7$, then R^4 is not hydrogen.

2. Compounds as claimed in claim 1 and in addition those in which R^2 may also represent a benzhydryl group, Y may also represent an alkoxy carbonyl group of the formula COOR where R represents a hydrogen atom or a lower alkyl group, or Y may also represent an amido group of formula $CONR^5R^6$ in which R^5 and R^6 are as defined in claim 1 and physiologically acceptable addition salts thereof.

3. 5 - {2 - [(1 - Methyl - 3 - phenylpropyl)amino]ethyl}salicylic acid, methyl ester hydrochloride.

4. 5 - {2 - [(1 - Methyl - 3 - phenylpropyl)amino]ethyl}salicylamide hydrochloride.

5. 5 - [2 - (Benzylamino)ethyl]saligenin acetate (salt).

6. 5 - (2 - Aminoethyl) - saligenin.

7. 5 - [2 - (α - Methyl - 3,4,5 - trimethoxyphenethyl)amino] ethyl saligenin acetate (salt).

8. 5 - [2 - Benzylamino)propyl]saligenin acetate (salt).

9. 5 - (2 - Aminopropyl) saligenin acetate (salt).

10. 4 - (2 - Aminoethyl) saligenin acetate (salt).

11. 4 - {2 - [(1,1 - Diphenylmethyl) - amino]ethyl}saligenin.

12. [5 - (2 - Aminopropyl) salicyl]urea.

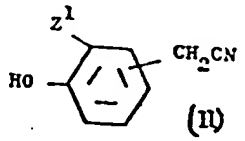
13. [5 - (2 - Aminoethyl) - 2 - hydroxy - phenyl]urea hydrochloride.

14. N - [5 - (2 - Aminopropyl)salicyl] - methanesulphonamide.

15. 5' - {[(3 - p - Methoxyphenyl - 1 - methylpropyl)amino]ethyl} - 2' - hydroxy - formanilide.

16. 4 - (2 - Benzylaminopropyl)salicylic acid methyl ester, hydrochloride.

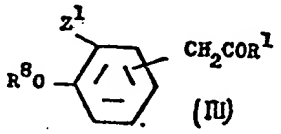
17. A process for the preparation of compounds as claimed in claim 1 or claim 2 which comprises (1) for the production of compounds in which R^1, R^2 and R^3 are hydrogen, reducing a nitrile of the formula II below



(II)

in which Z^1 represents a group Z or a group convertible thereto to produce a compound of formula I in which R^1, R^2 and R^3 are hydrogen atoms, which may subsequently be converted into compounds in which R^3 is other than hydrogen by reductive alkylation with an aldehyde or ketone providing said group R^3 or

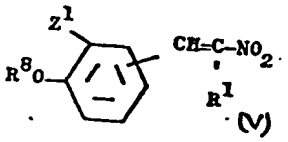
(2) for the production of compounds in which R^1, R^2 and R^3 have the meanings given in claim 7 condensing a carbonyl compound of the formula



(III)

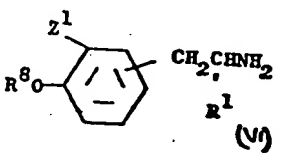
in which Z^1 has the meaning given above with an amine of the formula R^2R^3NH and reducing the resulting imine (in which R^8 represents hydrogen or a benzyl, lower alkyl or acyl group) with subsequent replacement of the said group R^8 where this is a benzyl, lower alkyl or acyl group and if necessary subsequently reducing the compound in which R^2 and R^3 are benzyl to give compounds in which these groups are hydrogen.

(3) for the production of compounds in which R^2 and R^3 are hydrogen, reducing a compound of the general formula



(V)

in which R^8 and Z^1 has the meaning given above, with subsequent removal of the group R^8 where this is other than hydrogen to give compounds of the formula

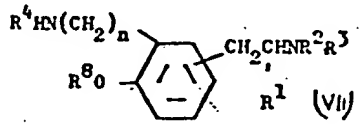


(VI)

and for the production of compounds in which R^3 is other than hydrogen subsequent reductive alkylation with an aldehyde or ketone providing said group R^3 followed in

each case if desired by conversion of the group Z^1 if other than Z to a group Z and if desired conversion of said group Z to another group Z within the meaning given in claim 1 the product if desired being isolated as the acid addition salt.

18. A process as claimed in claim 17 for the production of compounds in which the group Z represents a group $—(CH_2)_nNR^4COR^5$ in which R^4 and R^5 represent hydrogen atoms or lower alkyl groups which comprises acylating a compound of the formula



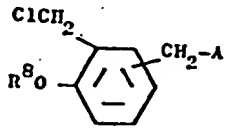
(VII)

in which R^1, R^2 and R^3 have the meanings given above except that R^2 and R^3 do not represent hydrogen, and R^4 is hydrogen, benzyl or lower alkyl, with an acid halide, ester or anhydride of an acid of the formula R^5COOH.

19. A process as claimed in claim 17 for the production of compounds in which Z is the group $—(CH_2)_nNR^4SO_2R^7$ or $—(CH_2)_nNR^4CONR^5R^6$, in which the compound of formula VII (R^2 and R^3 do not represent hydrogen) given in claim 17 is reacted with a sulphonyl chloride R^7SO_2Cl or a carbamoyl chloride R^5R^6NCOCl respectively, with subsequent replacement of the group R^4 by hydrogen when it is other than hydrogen.

20. A process as claimed in claim 7 for the production of compounds in which Y is $NR^4CONR^5R^6$ in which one or both R^5 and R^6 represent hydrogen in which the compound of formula VII defined in claim 18 in which R^2 and R^3 do not represent hydrogen is acylated with an alkyl cyanate of the formula R^5NCO, for the production of compounds in which R^6 is hydrogen, and for the production of compounds in which both R^5 and R^6 are hydrogen, with alkali metal cyanates.

21. A process as claimed in claim 17 in which the group convertible to Z is a halomethyl group and this is converted to a group $CH_2NR^4SO_2R^7$ in which R^4 has the meaning given but is other than hydrogen and R^7 has the meaning given which comprises reacting a compound of the formula



(XI)

(where $A=CHR^1NR^2R^3$ in which $R^1—R^3$ have the meanings given in claim 1) with an alkali metal salt of an N-alkylsulphonamide of the formula $R^7SO_2NHR^4$ and for the production of compounds in which R^4 is hydrogen reacting a compound of formula (XI) with the sodium salt of an acylsulphonamide R^7SO_2NHAc where Ac is an acyl group, with subsequent removal of any of the acyl and any other protective groups, and if desired with conversion of the group $CH—NR^2R^3$ to

other group by methods defined in claim 16.

22. A process for the preparation of compounds as claimed in claim 1 or claim 2 substantially as herein described with reference to the Examples.

23. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 17 to 21.

24. Pharmaceutical compositions comprising a compound as claimed in claim 1 in association with a pharmaceutically acceptable carrier.

25. Compositions as claimed in claim 4 adapted for oral administration.

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